**Abbreviated Title:** Effects of leptin in insulin resistance
**NIH IRB #:** 03-DK-0257
**Version Date:** 05/05/2021

**Title:** Phase II Trial of Effect of Metreleptin Therapy in Severe Insulin Resistance

*Principal Investigator:*

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**Investigational Agents** *(if applicable)***:**

| | |
|---|---|
| Drug Name: | Metreleptin |
| IND Number: | 60,534 |
| Sponsor: | NIDDK |
| Manufacturer: | Amryt Pharma, PLC |

**Multi-institutional protocols are protocols in which non-exempt human subjects research is taking place at more than one site. For multi-institutional protocols in which the intramural NIH IC is the Coordinating Center and/or Sponsor:** N/A

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## STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

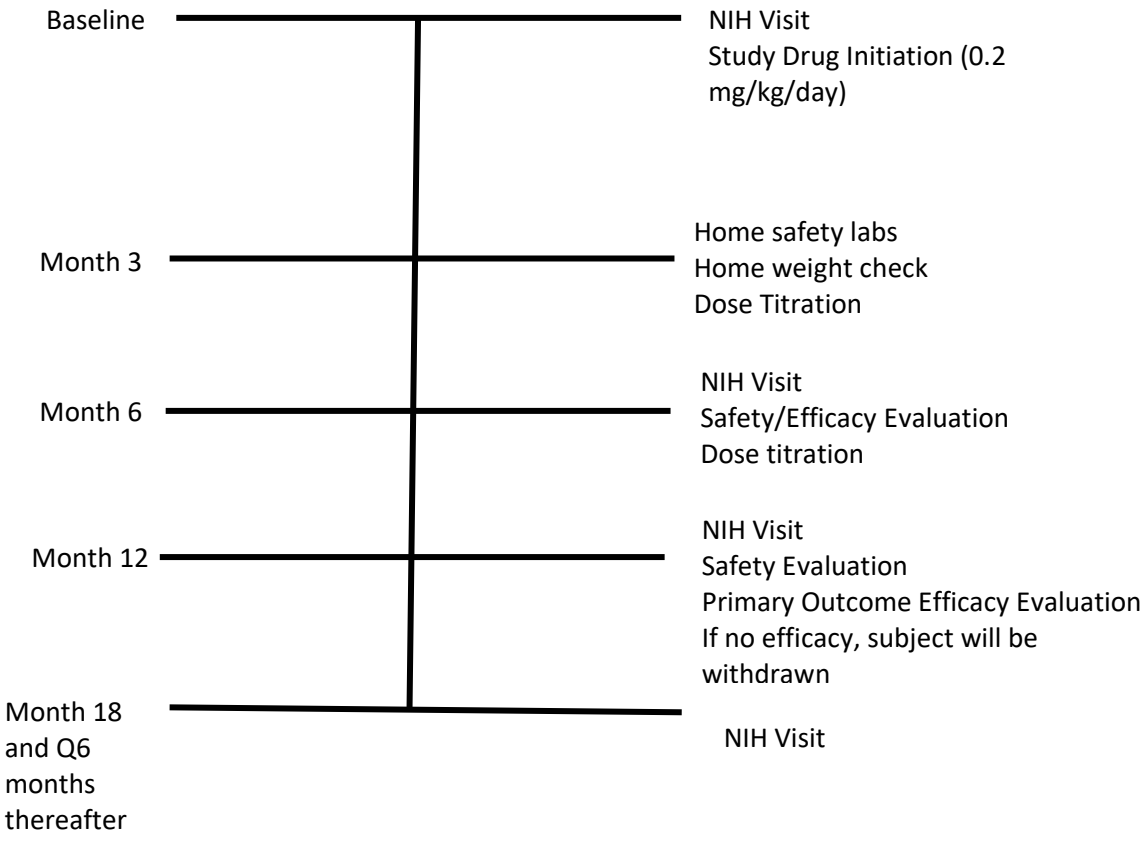
The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

# 1 PROTOCOL SUMMARY

## 1.1 SYNOPSIS

| | |
|---|---|
| **Title:** | Phase II Trial of Effect of Leptin Therapy in Severe Insulin Resistance |
| **Study Description:** | Patients with mutations of the insulin receptor have diabetes that is challenging to control with conventional therapies, leading to early morbidity and mortality. We hypothesize that recombinant leptin (metreleptin) in these patients will improve glycemia control. |
| **Objectives:** | Primary Objective: To determine if 1 year of metreleptin will improve glycemia control in patients with genetic defects of the insulin receptor. Secondary Objectives: To determine mechanisms by which metreleptin improves glycemia. |
| **Endpoints:** | Primary Endpoint: Hemoglobin A1c.<br>Secondary Endpoints: fasting plasma glucose, fasting insulin/C-peptide, glucose/insulin/C-peptide area under the curve during oral glucose tolerance test. |
| **Study Population:** | 20 male or female patients with mutations of the insulin receptor, age ≥5 years, at the NIH Clinical Center |
| **Phase:** | 2 |
| **Description of Sites/Facilities Enrolling Participants:** | NIH Clinical Center |
| **Description of Study Intervention:** | Open label study of metreleptin, 0.2 mg/kg/day (max dose 0.24 mg/kg/day). |
| **Study Duration:** | Indefinite as long as patients demonstrated benefit |
| **Participant Duration:** | 12 months (may be extended if patient demonstrates benefit) |

## 1.2 SCHEMA


Baseline
NIH Visit
Study Drug Initiation (0.2 mg/kg/day)
Month 3
Home safety labs
Home weight check
Dose Titration
Month 6
NIH Visit
Safety/Efficacy Evaluation
Dose titration
Month 12
NIH Visit
Safety Evaluation
Primary Outcome Efficacy Evaluation
If no efficacy, subject will be withdrawn
Month 18 and Q6 months thereafter
NIH Visit

## 1.3 SCHEDULE OF ACTIVITIES (SOA)

Baseline Visit (3-4 days): Patients will be admitted to the research center.
They will have their history and physical examination completed on the day of admission. Following a 12 hour fast, the OGTT will be performed. In addition, patients' capillary blood glucose will be measured before each meal and at bedtime. 24-hour glucosuria (and other 24 hour urine studies) will also be determined. After baseline testing has completed, patients will be trained in the proper storage, preparation, and administration of metreleptin injection, and will begin metreleptin injections subcutaneously during the hospitalization. Therapy will begin at determined efficacious dose for this group of patients of (0.2 mg/kg/day for male and female patients). For patients who reside outside the US, sufficient drug supply will be sent home with the patient to last until the next scheduled visit. For patients who reside within the US, a 3 month supply of drug will either be sent home with the patient or shipped to the patient's home.

Months 6 and 12 and every 6 months thereafter (3-4 days): At the end of 6 months, patients will return to the Clinical Center for collection of the same data obtained at baseline. For patients for whom it is challenging to travel to the Clinical Center every 6 months (i.e. ex-US patients), visits may be conducted every 12 months after the first year per investigator discretion. In the event that circumstances beyond our control preclude the travel of one or more of the study participants to the NIH Clinical Center for a visit, or otherwise would put their health at greater risk (i.e. epidemic or pandemic), we will endeavor to establish capabilities for remote visits. Specifically, the study team will request local laboratory studies to be done, to include, at a minimum, basic chemistry panel, CBC with diff, hemoglobin A1c, and pregnancy testing in female subjects with reproductive capacity, and conduct a telehealth/telephone visit with the patient. Telehealth/telephone visits will adhere to HHS guidance (https://www.hhs.gov/hipaa/for-professionals/special-opics/emergencypreparedness/notification-enforcement-discretion-telehealth/index.html) and can use all telehealth modalities under the good faith provision during a pandemic/epidemic as allowed by HHS for care of study participants.

At each follow up visit, for patients who reside outside the US, sufficient drug supply will be sent home with the patient to last until the next scheduled visit. For patients who reside within the US, a 3 month supply of drug will either be sent home with the patient or shipped to the patient's home (US patients only).

Unscheduled visits, due to safety or clinical care, may also be conducted remotely through telehealth/telephone and may include offsite laboratory and radiologic studies and/or in conjunction with a local physician with the supervision of the study PI. Laboratory and imaging results will be sent to the study team for safety monitoring and clinical care. During a pandemic affecting patient travel, serial missed research collections will not be considered major study deviations and will be reported to the IRB at the time of continuing review. Laboratory and imaging results obtained outside of the NIH may be incorporated into the study data set for both safety and efficacy.

During this time, patients remain on the full predicted dose. At each of these subsequent visits, the patients will have their blood drawn collecting the same labs that were obtained at baseline, and including serial metabolic testing such as the OGTT.

If after 12 months of treatment it is determined by the principal investigator that the patient has shown improvement metabolically (improved HgbA1c, FBS, fasting insulin level), we will continue to follow the patient indefinitely on leptin therapy until such time that the leptin is approved through the FDA and/or the patient does not wish to continue on the study.

The study will involve an initial week hospitalization for each recruited patient. Thereafter, the patients will return to the Clinical Center as in-patients for assessment and data collection in accordance with the program every 6-12 months. Pre-existing glucose lowering therapies will be adjusted as needed to prevent hypoglycemia per standard clinical practice by communication between qualified study staff and the patient (telephone, telehealth, etc.). Patients taking insulin are asked to check their blood sugars at least 2 times a day (before breakfast and before another meal or at bedtime). Patients not taking insulin are not asked to routinely monitor their glucose levels while at home.

| **Procedures** | Baseline | 6 months | 1 year | Q6 months (after 1st year) | Q12 months (after 1st year) |
|---|---|---|---|---|---|
| Informed consent | x | | | | |
| Demographics | x | | | | |
| Diabetes antibodies | x | | | | |
| Medical/interim history | x | x | x | x | X |
| Physical exam (including height and weight) | x | x | x | x | X |
| Vital signs | x | x | x | x | X |
| Height | x | x | x | x | X |
| Weight | x | x | x | x | X |
| Leptin level | x | x | x | x | X |
| Fasting labs (glucose, insulin, C-peptide, HbA1c, chemistry, CBC/diff, hormones, bone turnover markers, inflammatory markers) | x | x | x | x | X |
| Oral glucose tolerance test | x | x | x | | x |
| Pelvic ultrasound | x | x | x | | x |
| Thyroid ultrasound | x | x | x | | x |
| 24 hour urine studies | x | x | x | x | x |

# 2 INTRODUCTION

## 2.1 STUDY RATIONALE

Patients with extreme insulin resistance caused by biallelic pathogenic variants of the insulin receptor (Rabson Mendenhall syndrome) develop diabetes in childhood that is difficult to control with FDA-approved therapies, including insulin doses 50-fold higher than those typically used to treat diabetes. Thus, novel therapies that lower blood glucose independent of insulin-receptor signaling are needed. Recombinant human leptin (metreleptin) lowers blood glucose in patients with lipodystrophy and low leptin levels. Patients with Rabson Mendenhall syndrome also have low leptin as a result of low body fat (because insulin signaling is critical for adipogenesis), and thus are candidates for metreleptin therapy. In addition, the intracellular signaling cascades of leptin and insulin receptors overlap at PI3 kinase, suggesting that pharmacologic overstimulation of the leptin receptor might trigger intracellular insulin signal transduction. We therefore plan to test the safety and efficacy of metreleptin in patients with Rabson Mendenhall syndrome/

## 2.2 BACKGROUND

Type 2 diabetes is the most common form of diabetes, characterized by insulin resistance with inadequate compensatory insulin secretion, resulting in hyperglycemia. While type 2 diabetes is polygenic, there exist rare, monogenic conditions that cause severe forms of insulin resistance and diabetes. We have studied the more unusual syndromes of diabetes that are characterized by extreme forms of insulin resistance. All of these patients manifest severe hyperinsulinemia or have requirements for very large doses of insulin. The syndromes have been categorized under a variety of names. These include the following: type A insulin resistance and type B insulin resistance, which were first described in the NIDDK, and are characterized by abnormalities in the insulin receptor[i,ii]. Other syndromes of a similar nature include the Rabson-Mendenhall syndrome and the various syndromes of lipodystrophy.

Therapy for all of these syndromes has been inadequate and the prognosis and mortality rate for all of these syndromes has been extremely high. We have been following a group of patients with severe insulin resistance due to mutations on their insulin receptor gene. A fraction of these patients are compound heterozygotes or homozygotes for a mutation in the insulin receptor gene. In addition to having diabetes that is very difficult to control starting at young ages, these patients also have a paucity of fat. Low leptin levels (leptin levels <3.0 ng/mL) is an observed metabolic abnormality in this group of patients among other findings (unpublished observations). These most severe patients have very limited longevity (some die before age 10 years and others die before age 30 from multiple etiologies starting from severe diabetic complications to pulmonary hypertension and heart failure).

In a pilot study of two patients with the Rabson-Mendenhall syndromes (caused by biallelic mutations of the insulin receptor), 02-DK-0060, “Efficacy of leptin therapy in severe insulin resistance: a pilot study,” we followed two children with Rabson-Mendenhall on 10 months of recombinant leptin therapy. During the 10 months of leptin therapy, the patients had dramatic improvements (40%) in their fasting hyperinsulinemia and (50%) hyperglycemia, and overall improvements in their %HgbA1c and glucose and insulin tolerance. Three months after the medication was withdrawn, the improvements observed had deteriorated to their pre-trial baseline [1]. A follow up report published in 2013 in 5 patients who participated in the current study demonstrated that A1c decreased from 11.4±1.1% at baseline to 9.3±1.9% after 6 months and

9.7±1.6% after 12 months of metreleptin (P=0.007) [2]. In patients treated for 10 years, A1c declined with each cycle of metreleptin and rose with each withdrawal.

## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 Known Potential Risks

Risks of Metreleptin:

Metreleptin was FDA-approved to treat the complications of leptin deficiency in patients with congenital and acquired lipodystrophy in 2014. Potential risks of metreleptin based on studies in patients with generalized and partial lipodystrophy, obesity, and other populations are summarized in the Prescribing Information (http://www.myalept.com/prescribing-information).

Key potential side effects are summarized below:

1. Injection site reactions: The most frequently reported adverse events in studies of metreleptin have been skin reactions (injection site reactions) at the site where the drug is injected. injection site reactions of erythema, pruritus, inflammation (induration), urticaria and edema were reported in 40% of subjects from the previous studies (compared to 15% of placebo-treated subjects) (Investigator's Brochure). The majority were reported as mild in severity with average time of onset of 15 days. All sites of injection (abdomen, arm and leg) used for the site of injection were affected. Higher doses appeared to have greater incidence and earlier onset (Investigator's Brochure). Biopsies of the injection site have been reported in the Investigator's brochure from 2 cases. The results were similar and consistent with a delayed hypersensitivity reaction to the protein (Investigator's Brochure).

   Mild to moderate injection site ecchymosis was reported in 56% of all subjects, with a higher incidence occurring with subcutaneous bolus administration (as planned in this study) as opposed to administration with continuous infusion. There were no reported systemic symptoms to suggest a systemic allergic reaction. Some of the local reactions have been moderated with antihistamines, anti-inflammatory agents, topical steroids and cold compresses. In some subjects, investigators have reported gradual decreases in severity over time to complete disappearance of injection site reactions during continuous study-drug administration (Investigator's Brochure).

2. Hypersensitivity: Hypersensitivity reactions (e.g. anaphylaxis, urticaria, generalized rash) have been observed. Subjects who have a known history of anaphylaxis or anaphylactic-like reactions should not be administered Metreleptin. Also, subjects who have a known hypersensitivity to E. Coli derived proteins should not be administered Metreleptin because the Metreleptin protein is expressed in an E. Coli system.

3. Antibodies to recombinant human leptin: Development of anti-drug antibodies occurs in the majority of patients treated with metreleptin. In rare cases (<5%), antibodies with in vitro neutralizing activity to leptin may occur. Neutralizing antibodies could inhibit endogenous leptin action and/or result in loss of metreleptin efficacy.

4. Hypoglycemia: Metreleptin administration may increase the risk of hypoglycemia in patients treated with insulin or insulin secretagogues by improving insulin sensitivity. Patients will be cautioned about the possibility of hypoglycemia and all patients will receive education about signs and symptoms of hypoglycemia within the first week of the study

spent in the hospital. Diabetic patients will be measuring their glucose concentrations four times a day throughout the study and background therapy will be tailored to prevent hypoglycemia. Also we will explain this potential risk to the local physicians caring for the patients.

5. T-cell lymphoma: T-cell lymphoma has occurred in patients with acquired generalized lipodystrophy, both with and without metreleptin treatment. There is no data to support an increased risk of T-cell lymphoma (with or without metreleptin) in patients with mutations of the insulin receptor who may participate in this study.

6. Autoimmunity: Autoimmune disorder progression has been observed in patients with lipodystrophy treated with metreleptin, although a causal relationship with metreleptin has not been established. There is no data to support an increased risk of autoimmunity or autoimmune disease progression (with or without metreleptin) in patients with mutations of the insulin receptor who may participate in this study.

7. Papillary thyroid carcinoma: While on metreleptin therapy, three patients with severe insulin resistance due to either lipodystrophy or mutations of the insulin receptor developed papillary thyroid cancer. Another three patients with severe insulin resistance (again, lipodystrophy or insulin receptor mutations) developed papillary thyroid cancer but were never treated with metreleptin. Papillary thyroid cancer is a common cancer, and thus it is not yet clear if we are observing a true increased incidence, or if this represents population background risk, plus increased detection due to screening. There are epidemiologic data from patients with obesity or type 2 diabetes suggesting that insulin resistance may be a risk factor for papillary thyroid cancer. We do not know if metreleptin can promote growth of papillary thyroid cancer. Since patients with insulin resistance may be at higher risk for developing papillary thyroid cancer, we will screen subjects for this using ultrasound. They will have an ultrasound of their thyroid performed with their baseline visit, and at routine NIH follow-up visits if clinically indicated.

8. Weight loss: Metreleptin frequently leads to weight loss, particularly at the high doses used in this study. Body weight will be monitored per protocol, and doses of metreleptin adjusted to avoid severe weight loss.

9. Hair loss: 3 patients with lipodystrophy noted hair loss on metreleptin. The hair loss was a small amount, but the patients noticed it was a little more than what is typically lost in one day (around 100 hairs). One of the three patients noted the hair loss started before she started metreleptin. Two other patients on the study had significant hair loss, years before they started the study, to the extent that they need to wear wigs. It is not known if hair loss was related to metreleptin, part of the syndrome of lipodystrophy, or associated with insulin resistance and hormonal imbalances.

10. Other: Other frequently reported adverse events have been headache, fatigue, nausea and influenza-like symptoms. With the studies conducted so far, there have been no consistent patterns of changes noted in hematological parameters, ALT, AST, BUN, albumin and CPK values.

**OTHER RISKS:**
The total amount of blood drawn from the patients will be kept within the NIH Clinical Center restrictions. In adult patients, total amount of blood to be drawn with the outlined studies is estimated not to exceed 200 cc per 6-week period, which is well below the Clinical Center limit of 550 cc per 8-week period for research patients. Adjustments will be made in blood volumes for pediatric patients as necessary not to exceed the limit set by the following formula: (body weight (kg) x 9.5) cc blood per 8-week period.

Each blood draw is associated with pain and risks of infection though these risks are minimal. In routine care, the frequency of scheduled blood draws for any stable diabetic patient with current standards is at least 2-4 times a year. In this study, patients are asked to have a blood draw every 6-12 months.

The oral glucose tolerance test may cause nausea and requires placement of an IV catheter for blood draws. Ultrasound tests are not associated with any risk other than the discomfort of an ultrasound probe over a full bladder in female patients undergoing pelvic ultrasonography.

Some patients may find the time needed to complete the research studies an inconvenience in their routine lives. Each participant in the study will clearly understand that participation is totally voluntary.

Another source of inconvenience involved in this study is the necessity of 24-hour urine collections. However, this will facilitate assessment of long-term glucose control without the lag time that is usually observed with relying on HbA1c values.

### 2.3.2 Known Potential Benefits
Since the patients included in this protocol have metabolic abnormalities, they have some likelihood of clinical benefit from this trial. Patients have abnormalities causing a severe state of insulin resistance and often diabetes. Improvements in the patients' insulin sensitivity also have repercussions in improving patients' risks for diabetes. If patients have already had diabetes, improvements in insulin sensitivity can improve their diabetes control, and thus potentially reduce secondary complications normally seen in patients with Type 2 diabetes (heart disease, retinopathy, kidney disease).

Furthermore, the collected data may be used to answer some relevant clinical and basic questions involved in the disease processes. Therefore, there is a chance that future patients may also benefit from the results of this study.

### 2.3.3 Assessment of Potential Risks and Benefits
Our 20 year experience with metreleptin in patients with mutations of the insulin receptor and lipodystrophy shows that the risk profile of this drug is generally mild and manageable. Patients with mutations of the insulin receptor who are treated in this study have the potential for benefit from improved diabetes control, leading to lower risk of blindness, kidney failure, and amputation.

# 3 OBJECTIVES AND ENDPOINTS

| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
|---|---|---|
| Primary | | |
| To determine if metreleptin will improve glycemia control in patients with genetic defects of the insulin receptor. | Hemoglobin A1c | Hemoglobin A1c is a standard measure of efficacy of diabetes interventions, which correlates with risk of microvascular complications of diabetes. |
| Secondary | | |
| To determine mechanisms by which metreleptin improves glycemia. | Fasting glucose, insulin, and C-peptide; glucose, insulin, and C-peptide area under the curve after oral glucose tolerance testing (OGTT) | Fasting and post-OGTT glucose, insulin, and C-peptide provide additional measures of glycemia, beta-cell function, and insulin resistance. |
| Tertiary | | |
| To determine mechanisms by which leptin signals starvation and nutrient repletion | Body weight, body composition, creatinine clearance, urine 24-hour protein, hypothalamic pituitary function | These endpoints will offer insight into mechanisms by which leptin affects appetite and hormonal signals of starvation and nutrient repletion. |

# 4 STUDY DESIGN

## 4.1 OVERALL DESIGN

This study is designed to investigate the effect of recombinant leptin on various metabolic and hormonal abnormalities in patients with known or suspected mutations of the insulin receptor gene. These patients have low leptin levels in addition to other metabolic abnormalities. This study utilizes an open-label design, and the accrual ceiling is set at 20 patients. Cumulative changes in each patient will be compared to his/her baseline state after 6 and 12 months. The primary outcome will be assessed after 12 months of study drug. After the patient has completed one year of therapy and has shown metabolic improvement on the medication and the patient desires to continue therapy, the PI at NIH will consider extending therapy on an annual basis. The study medication is supplied through Amryt Pharma, and neither NIH nor Amryt Pharma can guarantee its availability after the study ends.

## 4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Given the extreme rarity of mutations of the insulin receptor, a placebo-controlled study is not feasible. Hence, an open-label within subjects design has been chosen.

### 4.3 JUSTIFICATION FOR DOSE

Subjects will be begin at a determined efficacious dose for this group of patients of 0.2 mg/kg/day for both female and male subjects.

## 5 STUDY POPULATION

### 5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Male or female, aged ≥ 5 years.
3. Clinically significant, severe insulin resistance caused by a known or suspected defect in the insulin receptor.
4. Presence of at least one of the following metabolic abnormalities:
    a) Fasting insulin >30 μU/ml, or
    b) Presence of diabetes as defined by the 2006 ADA criteria:
        i. Fasting plasma glucose ≥ 126 mg/dL
        ii. 2 hour plasma glucose ≥ 200 mg/dL following a 75 gram (1.75g/kg if less than 40kg) oral glucose load, or
        iii. Diabetic symptoms with a random plasma glucose ≥ 200 mg/dL
5. Ability of subject Legally Authorized Representative (LAR) to understand and the willingness to sign a written informed consent document.

### 5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Pregnant at time of enrollment, women in their reproductive years who do not use an effective method of birth control, and women currently nursing or lactating within 6 weeks of having completed nursing.
2. Known infectious liver disease
3. Known HIV infection
4. Current alcohol or substance abuse
5. Active tuberculosis
6. Use of anorexiogenic drugs
7. Other conditions which in the opinion of the clinical investigators would impede completion of the study.
8. Subjects who have a known hypersensitivity to E. Coli derived proteins.

### 5.3 INCLUSION OF VULNERABLE PARTICIPANTS

***Children:*** Patients with mutations of the insulin receptor, particularly those with biallelic mutations causing Rabson Mendenhall Syndrome, typically develop diabetes in childhood, with death often occurring in the second or third decade of life. Because this is a pediatric condition, most patients enrolled in this study will be <18 years of age. Children <5 years of age may not enroll. In our experience with the younger children, we find that their participation in serial blood tests improves greatly when they are at least 5 years of age. Also, in our experience with the patients with mutations of the insulin receptor, their initial insulin resistance is manifested as

extreme hyperinsulinemia and hypoglycemia (rather than hyperglycemia) in the younger patients. We would not want to treat a young child experiencing chronic hypoglycemia.

***Pregnant Women, Fetuses, or Neonates:*** Pregnant subjects may not enroll in the study, and avoidance of pregnancy will be strongly encouraged. All pre-menopausal women included in the study will be asked to use an effective method of contraception. If necessary, a gynecology consultation will be obtained to assist the patients to choose an appropriate method of contraception. In addition, pregnancy is unlikely in many women with insulin receptor mutations due to severe hyperandrogenism or its treatment (e.g. oophorectomy). To our knowledge, 6 subjects with lipodystrophy have had a total of 9 pregnancies while taking metreleptin. These subjects were permitted to continue metreleptin during pregnancy for the following reasons. Pregnancy is very well known to cause worsening of insulin resistance. In subjects with lipodystrophy who have extreme insulin resistance at baseline, this worsening may make diabetes during pregnancy very difficult to manage. Poorly controlled diabetes during pregnancy carries substantial risk to the fetus, including fetal malformations, macrosomia and shoulder dystocia, and neonatal hypoglycemia. The mother also bears risks from poorly controlled diabetes, including both micro and macrovascular complications. In the known pregnancy cases, the following outcomes are known: Subject 1 had a pregnancy complicated by inadequately controlled diabetes, with a large for gestational age infant who had shoulder dystocia at delivery resulting in Erb's palsy. Subject 2 had a healthy, full-term infant. Subject 3 had 2 second trimester spontaneous abortions attributed to cervical incompetence. She subsequently had 2 full-term pregnancies with cervical cerclage, with healthy infants. Subject 4 had a healthy full-term or near-term infant. Subject 5 had a spontaneous first trimester abortion. Subject 6 had a healthy near-term infant.

Because of the lack of proven risks of metreleptin during pregnancy, and the potential risks of metreleptin withdrawal, should a patient become pregnant while taking metreleptin, metreleptin may be continued during pregnancy under the following circumstances:

1. The investigators feel that metreleptin withdrawal would constitute a harm to mother and fetus.
2. The patient understands that the effects of metreleptin in pregnancy are unknown and wishes to continue.
3. The patient receives prenatal care from a high-risk obstetrician experienced in managing diabetes during pregnancy. Management of diabetes must be the primary responsibility of the patient's local health care providers, although the NIH study team will provide advice as appropriate regarding metreleptin use and use of concentrated insulin (U-500) if necessary.
4. The patient and her local health care team agree to remain in close contact with the NIH study team and respond to requests for clinical information needed to document the course of pregnancy and its outcome.

***Decisionally Impaired Adults:*** Patients with mutations of the insulin receptor appear to have higher prevalence of cognitive impairment compared to the general population, perhaps caused by periods of prolonged, unrecognized hypoglycemia during early brain development. Therefore, it is possible that patients without capacity to consent might be candidates for this study. Because

there is a prospect for direct benefit, adults who are unable to give informed consent will be eligible.

***Prisoners:*** *N/A*

***NIH Employees:*** *N/A*

***Other vulnerable populations:*** *N/A*

### 5.4 LIFESTYLE CONSIDERATIONS

Diet and Exercise: A dietitian will see each patient at every visit to the Clinical Center. A simple assessment of typical diet, exercise frequency, intensity and duration will be recorded at each visit (including telehealth or telephone visits).

### 5.5 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

### 5.6 STRATEGIES FOR RECRUITMENT AND RETENTION

This is a single site study taking place only at NIH. We currently have enrolled 11 subjects and our anticipated accrual is 20. Patients will be recruited through the existing pool of extreme insulin resistant patients that are being followed on 76-DK-0006, "Natural History of Disorders of Insulin Resistance" Patients will also be recruited from referrals from the patients' physicians, through physician referrals fielded through the Patient Recruitment and Public Liaison Office, or, occasionally, by self-referral.

#### 5.6.1 Costs

No costs to subjects are anticipated.

#### 5.6.2 Compensation

The travel expenses (within the continental United States) of patients and one guardian (for pediatric patients) to the Clinical Center will be compensated. Protocol-related medical care and follow-up of patients throughout the study including the medication will be provided by the Clinical Center free of charge. Medical care for an unforeseen reaction directly caused by either the therapy or follow-up procedures will also be provided by the Clinical Center.

## 6 STUDY INTERVENTION

### 6.1 STUDY INTERVENTIONS(S) ADMINISTRATION

#### 6.1.1 Study Intervention Description

Metreleptin will be administered in this study under IND 60,543.

### 6.1.2 Dosing and Administration

Metreleptin will be administered twice a day (Q12H) by subcutaneous injection at an initial dose of 0.2 mg/kg/day for both female and male subjects. The total daily dose will be administered via subcutaneous injections in two equally divided doses (12 hours apart). After 1 year on the study, if clinical benefit is seen from leptin therapy, once daily injections may be initiated. If clinical deterioration occurs with once daily injections, the patient may be returned to twice daily injections.

#### *6.1.2.1 Dose Escalation*

N/A

#### *6.1.2.2 Dose Limiting Toxicity*

N/A

#### *6.1.2.3 Dose Modifications*

Patients will monitor body weight at home weekly for the first 3 months of treatment. In addition, weight is monitored at each follow up visit. Doses of metreleptin will be adjusted based on body weight to maintain a consistent dose of metreleptin within the range of 0.18-0.24 mg/kg/day. If body weight decreases by more than 15%, then a dose reduction (by 0.02 mg/kg/day) will be made. If a dose change is made, patients will monitor body weight at home monthly for the next 3 months and additional dose adjustments will be made as needed.

#### *6.1.2.4 Drug Administration*

See above

## 6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

### 6.2.1 Acquisition and Accountability

*Availability:*

Amryt Pharma, PLC, is supplying Metreleptin.

*Initial Drug Shipment and Re-Supply:*

A signed and completed Drug Request Form must be emailed, at least 5 days prior to the expected delivery date, to Amryt Pharma Supply Chain for approval and processing at Orders.GAP@aegerion.com. At the end of the study, and after full accountability is performed on study drug or site closure, study drug destruction will occur at NIH.

*Supply of Drug:*

The study test drug will be shipped to the investigator's institution and should be checked for amount and condition of the drug received. This data will be entered into the proof of receipt letter. The proof of receipt letter should be faxed to Amryt Pharma at the number indicated on the letter and the original retained in the pharmacy files.

### 6.2.2 Formulation, Appearance, Packaging, and Labeling

Metreleptin will be supplied as a glass vial containing a lyophilized cake, prepared in a formulation buffer consisting of 10 mM glutamic acid, 2% glycine, 1% sucrose, and 0.01% Tween 20 to pH 4.25. Upon reconstitution with 2.2 ml of bacteriostatic sterile water, the cake will yield a 5-mg/ml concentration of Metreleptin.

### 6.2.3 Product Storage and Stability

The study drug must be stored in a secure location under controlled conditions at the study site or pharmacy before dispensing to subjects. Metreleptin must be stored at 2-8$^{o}$ C prior to reconstitution. It is recommended that the refrigerator be connected to a back-up power source, and a temperature alert system. Amryt Pharma must be notified if any test material is exposed to excessive or uncontrolled temperatures; possible replacement of the affected material will be considered. Study staff must be instructed in proper storage of the study drug.

*Storage Temperature Monitoring:*
Records of the storage conditions should be maintained throughout the study by either a continuous temperature recording system, a regularly maintained temperature alarm system or by regular visual inspection of a calibrated thermometer placed inside the refrigeration unit.

*Expiration Dating:*
As per standard practice for experimental biologic pharmaceuticals, Amryt Pharma will conduct periodic stability assays to monitor product stability and determine appropriate expiration dating of the study drug. The appropriate Amryt Pharma representative shall communicate this information to the investigator.

### 6.2.4 Preparation

Each 5 mL vial of lyophilized metreleptin (11.3 mg/vial) will be reconstituted with room temperature Bacteriostatic Sterile Water immediately prior to infusion. To reconstitute, 2.2 mL of sterile water should be injected slowly down the inside wall of the vial using a syringe and needle. Then the vial should be gently swirled and inverted until the powder is completely dissolved. THE VIAL SHOULD NOT BE SHAKEN VIGOROUSLY. The solution of reconstituted metreleptin should be clear, colorless, and free of any floating particles. Once reconstituted with bacteriostatic sterile water, remaining metreleptin can be used for up to 72 hours. Latex-free syringes should be used for all procedures with the study drug. The final concentration once reconstituted is 5 mg/ml.

## 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

N/A

## 6.4 STUDY INTERVENTION COMPLIANCE

Adherence to study drug will be assessed by frequency of medication refill requests as well as documentation of medication use in the medical record.

## 6.5 CONCOMITANT THERAPY

If patients are on glucose lowering therapy at the beginning of the study, metreleptin will be added to the existing therapy. Patients' previous therapy will be tapered to prevent hypoglycemia if necessary but doses of glucose lowering medications will not be increased during the first year of the study (at the time the primary outcome is assessed.) Glucose lowering therapies may be adjusted as clinically indicated after the first year of treatment. Patients will be standard clinical instruction about signs and symptoms of and instructions to relieve hypoglycemia.

# 7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 DISCONTINUATION OF STUDY INTERVENTION

See section 7.2

## 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Adverse events that are not readily explained by other causes unrelated to current protocol. Examples include:
    - Systemic life-threatening allergic reaction to metreleptin
    - Other significant medical issues that will, in the judgment of the investigators, preclude safe completion of the study.
- Noncompliance with self-monitoring requirements and Clinical Center visits
- Development of any medical problem listed in the exclusion criteria
- Significant medical issues that will in the judgment of the investigators preclude safe completion of the study. If an investigator feels it is in the subject's best interest to terminate participation, the detailed reasoning behind this decision will be documented. Examples include change in benefit-risk ratio of metreleptin treatment for an individual patient, such as:
    - Loss of efficacy of metreleptin (e.g. due to development of neutralizing antibodies)
    - Development of a medical condition that might increase risks associated with metreleptin (e.g. T-cell lymphoma, high risk thyroid cancer) in a patient not receiving dramatic clinical benefit
    - More than 8% drop in hematocrit and discontinuation recommended by Hematology Service
    - WBC count < 2500 or absolute neutrophil count < 1000 and discontinuation recommended by Hematology Service
- Death

The reason for participant discontinuation or withdrawal from the study will be recorded in the medical record.

## 7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 1 scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 6 months and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 2 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

# 8 STUDY ASSESSMENTS AND PROCEDURES

## 8.1 SCREENING PROCEDURES

### *8.1.1 Screening activities performed prior to obtaining informed consent*

A waiver of consent (per section 10.1.1) is requested for the following screening activities as the following are minimal risk activities and can be performed before the subject has signed a consent:

- Email, written, in person or telephone communications with prospective subjects.
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images.
- Review of existing photographs or videos.
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes.

### *8.1.2 Screening activities performed after a consent for screening has been signed*

The following activities will be performed only after the subject has signed the consent this study. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

- Measurement of blood leptin concentration

## 8.2 EFFICACY ASSESSMENTS

1. Evaluation of diabetes control (7 mL): HbA1c, fasting C-peptide and insulin.

2. Oral Glucose Tolerance Test: After an overnight fast preceding the test, subjects will be given 75-gram (1.75gm/kg up to 44kg) oral glucose solution. Venous glucose, plasma insulin and C-peptide (3 cc blood to be drawn at each draw) will be obtained from blood samples drawn at -10, 0, 30, 60, 90, 120 and 180 minutes during the oral glucose tolerance test. The area under the glucose, insulin and C-peptide.

### 8.2.1 Clinical Evaluations

1. Diabetes related antibodies (4 cc; first visit only)

2. Physical Examination: This will be performed at each visit and will incorporate a standard physical examination with special emphasis on skin exam and dysmorphic features. Pubertal exam (including examination of breasts and external genitalia) will be performed as age appropriate.

3. Vital Signs: Height in cm, weight in kg and blood pressure, BMI, resting pulse, temperature in degrees Celsius.

4. Biochemical evaluation (3 cc): This will include basic chemistry, liver panel, and mineral panel and cystatin C.

5. Hematological evaluation (3 cc): This will include determination of CBC with differential white count analysis.

6. Urine studies: This will include urinalysis and 24 hr urine for protein, microalbuminuria, minerals, uric acid, creatinine and creatinine clearance.

7. Lipid profile (3 cc): Levels of fasting triglyceride, total cholesterol, LDL cholesterol, HDL cholesterol, lipoprotein profile, free fatty acid, and lipoprotein profile will be obtained. These will be drawn after an overnight fast.

8. Hormonal evaluation (12 cc): This will include measurement of ~~R~~reproductive hormones (i.e. sex steroids, gonadotropins), assessment of the growth hormone axis (i.e. IGF-1, GH, IGF binding proteins), bone health and turnover markers (i.e.osteocalcin, PTH, Vitamin D), thyroid function tests.

9. Inflammatory markers (2 cc): This will include ESR and hsCRP.

10. Leptin concentration (part of 10 cc research blood collection): Leptin concentrations will be determined will be done after a overnight fast.

11. Ultrasound of pelvis: This will be performed on the female patient to evaluate the effects of hyperinsulinism and hyperandrogenism on the uterus and ovaries.

12. Ultrasound of the thyroid: This will be performed to screen for possible papillary thyroid carcinoma (PTC) or other possible thyroid structural abnormalities since this patient population may be at a higher risk of developing PTC. The testing may also uncover information for future analysis. Subjects will have an ultrasound of their thyroid performed with their baseline visit and at routine NIH follow-up visits, as clinically indicated.

### 8.2.2 Biospecimen Evaluations

*Biological specimen collection and laboratory evaluations*
See Section 8.2 and 8.2.1 for details.

Research blood samples: The amount of blood that may be drawn from adult patients and volunteers (i.e., those persons 18 years of age or older) for research purposes shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period.

For pediatric patients, no more than 5 mL/kg may be drawn for research purposes in a single day, and no more than 9.5 mL/kg may be drawn over any eight-week period.

### 8.2.3 Correlative Studies for Research/Pharmacokinetic Studies

*Special assays or procedures required*
See Section 8.2.1 for leptin assays.

### 8.2.4 Samples for Genetic/Genomic Analysis

*8.2.4.1 Description of the scope of genetic/genomic analysis*
None

*8.2.4.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized*
N/A

*8.2.4.3 Management of Results*
N/A

*8.2.4.4 Genetic counseling*
N/A

## 8.3 Safety and Other Assessments

See Section 8.4

- Pregnancy tests will be performed at each visit in female patients with reproductive capacity.

Results of all clinical tests reported in the patient's NIH medical record and will be provided to and discussed with subjects.

## 8.4 Adverse Events and Serious Adverse Events

### 8.4.1 Definition of Adverse Event

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

### 8.4.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency

room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### 8.4.3 Classification of an Adverse Event

*8.4.3.1 Severity of Event*

The following guidelines will be used to describe AE severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

*8.4.3.2 Relationship to Study Intervention*

All adverse events (AEs) must have their relationship to study intervention assessed by the investigator who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

*8.4.3.3 Expectedness*

The PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

### 8.4.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit.

Study staff will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

*Laboratory Test Result Abnormalities*
The following laboratory test result abnormalities will be captured as non-serious AE or SAE as appropriate:

1. Any laboratory test result that is clinically significant or meets the definition of an SAE
2. Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
3. Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

### 8.4.5 Adverse Event Reporting

It is both the Principal Investigator's (PI) and the Sponsor's responsibility to ensure the safety of those on the clinical trial. The PI is responsible for tracking adverse events during the study and providing adverse events lists to the Sponsor at regular intervals per request. In addition, the PI is responsible for updating the Sponsor about known risks from the drug, as discovered from literature searches or other means. Adverse events will be reported in accordance with the NIH Office of Human Subjects Research Protection policy #801.

### 8.4.6 Serious Adverse Event Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 30 days of discontinuation of dosing. The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness. If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, (including pregnancies) must be reported to United BioSource Corporation (UBC) (a contract research organization contracted by Amryt Pharma) on an SAE Report Form or similar form (e.g. CIOMS, MedWatch) and submitted as soon as possible but not more than 7 calendar days in the event of a death or a life-threatening event or in 15 calendar days for all other SAEs. The SAE report(s) and are to be transmitted via email or confirmed facsimile (fax) transmission to:

**SAE Email Address:** AmrytVP@ubc.com

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported). If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent to the United BioSource Corporation (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

Per NIH HRPP SOP 801, all serious adverse events will be reported to the IRB at the time of annual review if they do not meet the expedited reporting criteria. The PI will report all deaths per the NIH HRPP SOP #801.

In accordance with the requirements of 21 CFR 312.32, the PI or designee will report all SAEs, whether or not these are considered related to the investigational drug or study intervention, that occur throughout the study to the Sponsor, including those events listed in the protocol or Investigator's Brochure as anticipated to occur, as follows:

Deaths: within 24 hours of the investigator's awareness
All other SAEs: within 48 hours of the investigator's awareness
All AEs will be sent to the Sponsor quarterly, or at minimum annually, for submission to the FDA in the IND Annual Report.

The PI will immediately report all deaths and SAEs to the Sponsor by disclosing all event-related information in a completed MedWatch Form 3500A. This form should include the IND number, protocol number, PI name, and an assessment on the reasonable possibility of a relationship between the event and the study drug or intervention. The completed MedWatch Form 3500A will be sent to the Clinical Director/CEO and/or designated medical monitor with a copy to the NIH Office of Research Support & Compliance (ORSC) Regulatory Support Section.

The CEO and/or designee will be responsible for determining whether the event is reportable to the FDA as an IND Safety Report if it is a serious, unexpected, and suspected adverse reaction (SUSAR). If the sponsor determines the SAE meets the criteria of a SUSAR, the ORSC will submit an Initial IND Safety Report to the FDA no later than 15 calendar days after the PI's notification of the event to the Sponsor. Deaths or life-threatening events will be reported to the FDA no later than 7 calendar days after the PI's notification of the event to the Sponsor. The Sponsor will submit any relevant additional information in a Follow-up IND Safety Report no later than 15 calendar days after receiving the information. All SAEs will be monitored until satisfactory resolution. All AEs and SAEs will be documented on appropriate study records.

### 8.4.7 Events of Special Interest

*Overdose*

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

*Infectious agent transmission by investigational product*

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE. Although overdose and cancer, are not always serious by regulatory definition, these events will be handled as SAEs (per Amryt Pharma request).

### 8.4.8 Reporting of Pregnancy

Should a patient become pregnant while on study, per 45 CFR 46.204, (1) no inducements, monetary or otherwise, will be offered to terminate a pregnancy, (2) individuals engaged in research will not be involved in any decisions as to timing, method, or procedures used to terminate a pregnancy, and (3) individuals engaged in the research will have no part in determining viability of a neonate.

Pregnancies will be recorded on a United BioSource Corporation (UBC) Pregnancy Surveillance Form. The investigator will notify the Amryt Pharma via UBC (a contract research organization contracted by Amryt Pharma) (or designee) Medical Monitor of confirmed pregnancies and forward the Pregnancy Surveillance Form to UBC (or designee) within 7 business days of the PI is first notified of the pregnancy. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information will be reported on the Pregnancy Surveillance Form. Any pregnancy that occurs in a female partner of a male study participant should be reported to Amryt Pharma via UBC. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. Forms are to be transmitted via email to:

Email address: AmrytPV@UBC.com

## 8.5 UNANTICIPATED PROBLEMS

### 8.5.1 Definition of Unanticipated Problems (UP)

Any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others (which many include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or expected.

### 8.5.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the NIH Institutional Review Board (IRB) as per Policy #801.

### 8.5.3 NIH Intramural IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NIH Intramural IRB.

# 9 STATISTICAL CONSIDERATIONS

## 9.1 STATISTICAL HYPOTHESIS

- Primary Endpoint(s): The primary outcome measure is improvement in HbA1c after 1 year of metreleptin,
- Secondary Endpoint(s): A number of secondary endpoints will also be studied. These include fasting blood glucose, and insulin, and C-peptide levels, as well as the glucose, insulin, and C-peptide responses to glucose tolerance tests. In the pilot study, we have observed up to a 40% reduction in fasting blood glucose, and an even greater reduction in endogenous hyperinsulinemia. While we would hope to see changes of this magnitude we cannot pre-define the extent of improvement or lack thereof that may occur.
- Exploratory Endpoints: These include body weight, body composition, creatinine clearance, and urine 24-hour protein. In addition, we will include hypothalamic pituitary parameters, LH/FSH, and thyroid function.

## 9.2 SAMPLE SIZE DETERMINATION

Published data from 5 subjects who participated in this study [2] indicated the A1c change 6 months after treatment was about 2.1 with standard deviation of 1.4. Based on these data, a sample size of 6 will lead to a power of 80% (at a two-sided alpha of 0.05). A sample size of 7 would allow detection an A1c change of 2.0 with a standard deviation of 1.5.

## 9.3 POPULATIONS FOR ANALYSES

### 9.3.1 Evaluable for toxicity

All participants will be evaluable for toxicity from the time of their first treatment with metreleptin.

### 9.3.2 Evaluable for objective response

Data will be analyzed as Per-Protocol Analysis Dataset: including the subset of the participants who took at least 70% of study intervention.

### 9.3.3 Evaluable Non-Target Disease Response

N/A

## 9.4 STATISTICAL ANALYSES

### 9.4.1 General Approach

The patients are all analyzed as a function of their baseline metabolic status. Each patient is his/her own control against their own baseline data. The appropriate statistical analysis as applied in our study of lipodystrophic patients will be utilized. Under certain conditions student's t-test and ANOVA will be used. Under circumstances of data that is not distributed normally, log-transformations will be carried out.

### 9.4.2 Analysis of the Primary Endpoints

Primary endpoints will be analyzed as per the general analysis plan, above. Glucose and insulin area under the curve during oral glucose tolerance tests are calculated using the trapezoidal method.

### 9.4.3 Analysis of the Secondary Endpoint(s)
Secondary endpoints will be analyzed as per the general analysis plan, above.

### 9.4.4 Safety Analyses
All adverse events (AEs) will be captured, whether related to the study drug or not, and documented per the PI's discretion. The AE(s) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). In addition, the study team will also capture the event start date, stop date, severity, relationship to study drug, expectedness (per the Investigator Brochure), any associated treatment or hospitalization, and outcome. At the time of annual Continuing Review (CR), the AEs, that have occurred since the previous CR, will be reviewed by the PI and summarized (per the NIH SOP #801) within the CR submission Form. The same AEs included with the annual NIH CR will also be included in the FDA Annual Report.

### 9.4.5 Baseline Descriptive Statistics
N/A

### 9.4.6 Planned Interim Analyses
N/A

### 9.4.7 Sub-Group Analyses
N/A

### 9.4.8 Tabulation of individual Participant Data
Individual participant data may be listed by measure and time point.

### 9.4.9 Exploratory Analyses
This is not a registrational trial.

## 10 REGULATORY AND OPERATIONAL CONSIDERATIONS

### 10.1 INFORMED CONSENT PROCESS
### 10.1.1 Consent/Assent Procedures and Documentation
*Request for Waiver of Consent for Screening Activities:*
Prior to the subject signing the consent for this study, pre-screening activities listed in section 7.1.1 may be performed. We request a waiver of consent for these activities as they involve only minimal risk to the subjects. A waiver will not adversely affect the rights and welfare of the subjects given that the activities are only intended to determine suitability for screening for participation in research protocols. These activities could not practicably be carried out without the wavier as central recruiting services, utilized in the NIH Clinical Center, perform pre-screening activities for multiple studies and obtaining consent for each one is beyond their resources. The subjects will be provided with additional pertinent information after participation as they will be informed whether are or not they are eligible to sign a consent for additional screening.

Informed consent begins with the initial approach of an investigator to a potential subject (for example through a flyer or advertisement) and continues (a) until the completion of the research study, (b) until the individual completes study participation, (c) the subject withdraws him/herself from the study or (d) the subject is withdrawn from the study by the investigator. Written informed consent will be obtained from the participant prior to any screening visits, study procedures or treatments. The Principal Investigator or other designated qualified protocol investigators will explain the study in language understandable to the subject. Sufficient time and opportunity will be given for discussion of the research as well as to answer any questions they may have, taking care to minimize or eliminate the perception of coercion or undue influence. The participant and the investigator will sign the current IRB-approved informed consent document. A copy of the consent will be given to the subject for future reference. The signed documents will be sent to the Medical Records Department for placement in the subject's permanent CC medical record. The consent process will additionally be documented in the electronic medical record (CRIS).

*Consent/Assent Process for Minors/Children (under 18 years of age):*
Written informed consent and assent will be obtained from the minor and his/her parent(s)/guardian(s) or his/her LAR prior to any screening visits, study procedures or treatments. The Principal Investigator or other designated qualified protocol investigators will explain the study in language understandable to the parent(s)/guardian(s) or LAR. The parent(s)/guardian(s) or the LAR will sign the current IRB approved informed consent (in accordance with 45 CFR 46.408).

Where deemed appropriate by the clinician and the child's parent(s) or guardian, the child will also be included in all discussions about the trial and age-appropriate language will be used to describe the procedures and tests involved in this study, along with the risks, discomforts and benefits of participation. In general (depending on cognitive ability), verbal assent will be obtained for children ages 7-11, and children aged 12 and older will be asked to either sign the assent or adult consent form (within the Minor signature block). Children aged ≤ 6 will not be required to provide assent as they typically do not have the ability to fully understand the nature of research. The consent/assent process will be documented in the child's medical record, including the assessment of the child's ability to provide assent (verbal versus written, as assessed by the investigator) as applicable. All children will be contacted after they have reached the age of 18 to determine whether they wish to continue on the trial and informed consent will be obtained from them at that time. The investigator will sign the assent as well. A copy of the consent and assent will be given to the minor and his/her parent(s)/guardian(s) or the LAR for future reference. The signed documents will be sent to the Medical Records Department for placement in the subject's permanent CC medical record. The consent process will additionally be documented in the electronic medical record (CRIS).

*Consent process for Adults with Decisional Impairment:*
Because there is a prospect for direct benefit, adults who are unable to give informed consent will be eligible. The PI or AI will contact the NIH Ability to Consent Assessment Team(ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects

that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

### 10.1.2 Consent for minors when they reach the age of majority

When a pediatric subject reaches the legal age (i.e. 18 years of age), in order for the patient to continue receiving medical care without interruption, we plan to re-consent the patient to the study at their next scheduled NIH or telehealth visit using the same process we would use to consent an adult subject.

If reconsent is not feasible, we request waiver of informed consent to continue to use data and/or specimens for those individuals who become lost to follow up or who have been taken off study prior to reaching the age of majority.
Requirements for Waiver of Consent consistent with 45 CFR 46.116 (d):

(1) The research involves no more than minimal risk to the subjects.
    a. Analysis of samples and data from this study involves no additional risks to subjects.
(2) The research could not practicably be carried out without the waiver or alteration.
    a. Considering the length of time between the minor's last contact with the research team and their age of majority, it will likely be very difficult to locate them again. A significant reduction in the number of samples analyzed is likely to impact the quality of the research.
(3) The waiver or alteration will not adversely affect the rights and welfare of the subjects.
    a. Retention of these samples or data does not affect the welfare of subjects.
(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
    a. We only request a waiver of consent for those subjects who have been lost to follow-up or who have been taken off study prior to reaching the age of majority.

### 10.1.3 Telephone (or Telehealth) consent

In most cases, consent will be obtained during a visit to NIH. However, in some cases, consent will be obtained by telephone or by the NIH Telehealth system for patients who are already enrolled in the study, in whom updated consents/assents are needed.

If a telephone or Telehealth consenting process is performed, the written consent form will be mailed to the subject with a prepaid return envelope or sent electronically in advance of the telephone consent. The study team will arrange a time with the subject to conduct the telephone consent process. At this prearranged time, the PI or associate investigator (as listed on this protocol) will call the patient to review the details of the study to obtain the patient's verbal and written consent (by ink or electronic signature using a stylus, mouse or finger) to participate. The subject will sign the consent form and mail it to NIH, where it will be signed by the consenting investigator and filed in the patient's medical record and a copy will be mailed to the patient. If the subject signs by electronic signature (using a stylus, mouse or finger), once signed by the subject, the subject will email the signed consent via Secured Email or send by postal service to

the consenting investigator. The consenting investigator will then sign the consent (by ink or electronic signature using a stylus, mouse, finger) and file in the patient's medical record, and a copy will be securely emailed or sent by postal service to the patient. A note will also be filed in the patient's electronic record documenting the call/consenting process.

### 10.1.4 Telephone (or Telehealth) assent

The informed consent and assent documents will be sent to the parents/guardian and child. An explanation of the study will be provided over the telephone or telehealth after the parents/guardian and child have had the opportunity to read the documents. Age-appropriate language will be used to discuss the study with the child. The parents/guardian will sign and date (by ink or electronic signature using a stylus, mouse or finger) the informed consent. If an assent form is used (see above for when an assent form will be used), the child will sign and date (by ink or electronic signature using a stylus, mouse or finger) that form. If the subject signs by electronic signature (using a stylus, mouse or finger), once signed by the child, the subject's parent/guardian will email the signed consent via Secured Email or send by postal service to the consenting investigator. The consenting investigator will then sign the consent (by ink or electronic signature using a stylus, mouse, finger) and file in the patient's medical record, and a copy will be securely emailed or sent by postal service to the patient. All children will be contacted after they have reached the age of 18 to determine whether they wish to continue on the trial and informed consent will be obtained from them at that time.

### 10.1.5 Considerations for Consent of NIH employees

N/A

### 10.1.6 Consent of Subjects who are/become Decisionally Impaired

Because there is a prospect for direct benefit, currently enrolled adults who become unable to give informed consent will remain eligible. The PI or AI will contact the NIH Ability to Consent Assessment Team(ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH HRPP SOP 403 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

For patients currently enrolled on the protocol, that are turning of legal age (i.e. 18 years of age) and who are unable to provide consent, the same procedures described above will be used in order for the patient to continue receiving study drug without interruption. We will give adult subjects who are unable to consent the opportunity to assent, and we will respect subjects' wishes to dissent.

## 10.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and the FDA and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Determination that the primary endpoint has been met
- Determination of futility
- Unwillingness of Amryt Pharma to continue providing metreleptin for the study

## 10.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible. The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.
To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

## 10.4 FUTURE USE OF STORED SPECIMENS AND DATA

At each visit, 10 cc of blood will be drawn and stored for future research related to insulin resistance and its complications, or metreleptin treatment and its complications, including possible analysis of leptin antibodies.

For future reference and potential use, we will store all samples (blood and fluids) in our locked freezer for an unlimited period of time. Samples will be labeled with coded identifiers linked to patient identity only via a secured database. Research records and data with personal identifiers will be stored in our locked offices, the medical record department, and the electronic study database. This material will additionally be protected by medical record and computer access procedures.

Access to records and data associated with personal information will be restricted to the Principal Investigator, Co-Investigators, study support staff, and database support staff.

Stored samples and/or data may be sent to outside collaborating laboratories, or shared with other NIH collaborating investigators, to study questions related to lipodystrophy or its complications (including, for example: glucose metabolism, diabetes, obesity, weight, appetite, steatohepatitis, and lipid metabolism). Samples may be sent to outside commercial laboratories for analysis. Samples and data sent to outside laboratories and collaborators for analysis and/or testing will contain only coded numbers, without personal identifiers. Tech Transfer agreements will be completed before the exchange of samples and/or data with outside collaborators.

Subjects may request that unused samples be removed from our freezers and returned to the subject, or be destroyed. If no such request is made, we will keep samples until they are completely used or no longer of scientific value, at which time they will be destroyed. We do not plan to destroy personal medical information or stored data. The Principal Investigator will report loss or destruction of data or samples to the IRB. Data and samples will be retained for the foreseeable future in order to allow secondary analyses after the completion of the protocol.

### 10.5 Safety Oversight

It is both the Principal Investigator's (PI) and the Sponsor's responsibility to ensure the safety of those on the clinical trial. The collection, monitoring and analysis of adverse events will be the responsibility of the Principal Investigator and the investigative team. The PI is responsible for providing adverse events lists to the Sponsor at regular intervals per request. In accordance with the requirements of 21 CFR 312.32, the PI or designee will report all serious adverse events (SAEs) to the IRB per NIH guidelines and to the Sponsor. SAEs are to be reported whether or not they are considered related to the investigational drug or study intervention, that occur throughout the study to the Sponsor, and includes those events listed in the protocol or Investigator's Brochure as anticipated to occur. Overall accrual and adverse event information will be reported to the IRB annually. In addition, the PI is responsible for updating the Sponsor about known risks from the drug, as discovered from literature searches or other means.

### 10.6 Clinical Monitoring

Monitoring for this study will be performed by the NIDDK Quality Assurance Program.

### 10.7 Quality Assurance and Quality Control

The PI will conduct and supervise the protocol and provide appropriate delegation of responsibilities to the listed study Investigators once all required training is completed. The PI and study team will meet on a regular basis to discuss potential patients including the protocol-required tests each subject will need. The study team will also discuss any adverse events (AEs) they have learned of, as well as identify and correct any possible problem areas to avoid protocol deviations. The PI will oversee the data collected on subjects is performed per protocol guidelines, including the reporting of events within the specified timeframes per NIH SOPs and FDA guidance.

As required by FDA 21 CFR 312.50 (and NIH OHSRP's SOP 801), trial procedures will be subject to review and/or monitoring visits to ensure compliance with the protocol and applicable regulatory requirements with the NIDDK quality assurance program plan. Audit and/or monitoring visits results will be reported to the Principal Investigator/Sponsor for further reporting to the FDA and IRB consistent with applicable regulations. The specific monitoring plan will be developed with the Principal Investigator and frequency of monitoring visits determined by such factors as study enrollment, data collection status and regulatory obligations. Study documents and pertinent hospital or clinical records will be reviewed to verify that the conduct of the study is consistent with the protocol plan.

## 10.8 DATA HANDLING AND RECORD KEEPING

### 10.8.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Primary source data for this study will be the NIH medical record system (CRIS).

### 10.8.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention, or as per the NIH Intramural Records Retention Schedule.

## 10.9 PROTOCOL DEVIATIONS AND NON-COMPLIANCE

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations and/or non-compliance to the NIH Institutional Review Board as per Policy 801. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

### 10.9.1 NIH Definition of Protocol Deviation

A protocol deviation is any changed, divergence, or departure from the IRB-approved research protocol.

- Major deviations: Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
- Minor deviations: Deviations that do not have the potential to negatively impact the rights, safety or welfare of subjects or others, or the scientific integrity or validity of the study.

## 10.10 PUBLICATION AND DATA SHARING POLICY

### 10.10.1 Human Data Sharing Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-

reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested by other researchers upon reasonable request.

### 10.10.2 Genomic Data Sharing Plan

N/A

## 10.11 Collaborative Agreements

### 10.11.1 Agreement Type

Collaboration has been established with Professor Stephen O'Rahilly in Cambridge, England. Our direct physician contacts are Dr. Robert Semple (University of Edinburg) and Dr. David Savage (University of Cambridge). The purpose of this collaboration is to share coded clinical data and coded specimens collected from subjects enrolled under this protocol at NIH. The collaborators will assist in determining profiles of blood markers of insulin action, to look for causative genetic mutations in the insulin receptor gene and other genes that may cause severe insulin resistance, to study the functional significance of potentially causative mutations, and to improve the diagnosis of patients with syndromes of extreme insulin resistance by characterizing their phenotype. (DK#17-0903)

A Materials Cooperative Research and Development Agreement (m-CRADA) (DK#9918/1) was established 31/OCT/2001 with Amgen Pharmaceuticals. Over the years, the agreement was extended and amended as the drug manufacturer changed 6 times over the life of this study. We are currently working on amending the latest Clinical Research Agreement (CRA) with the current drug manufacturer, Amryt Pharma. The agreements were established, and extended, in order for subjects to receive the study drug, metreleptin, that the drug manufacturer provided. In addition, the agreement allowed the drug manufacturer to view and obtain coded subject data resulting from the research involving metreleptin, including event reports. The current CRA is DK#16-0661.

## 10.12 Conflict of Interest Policy

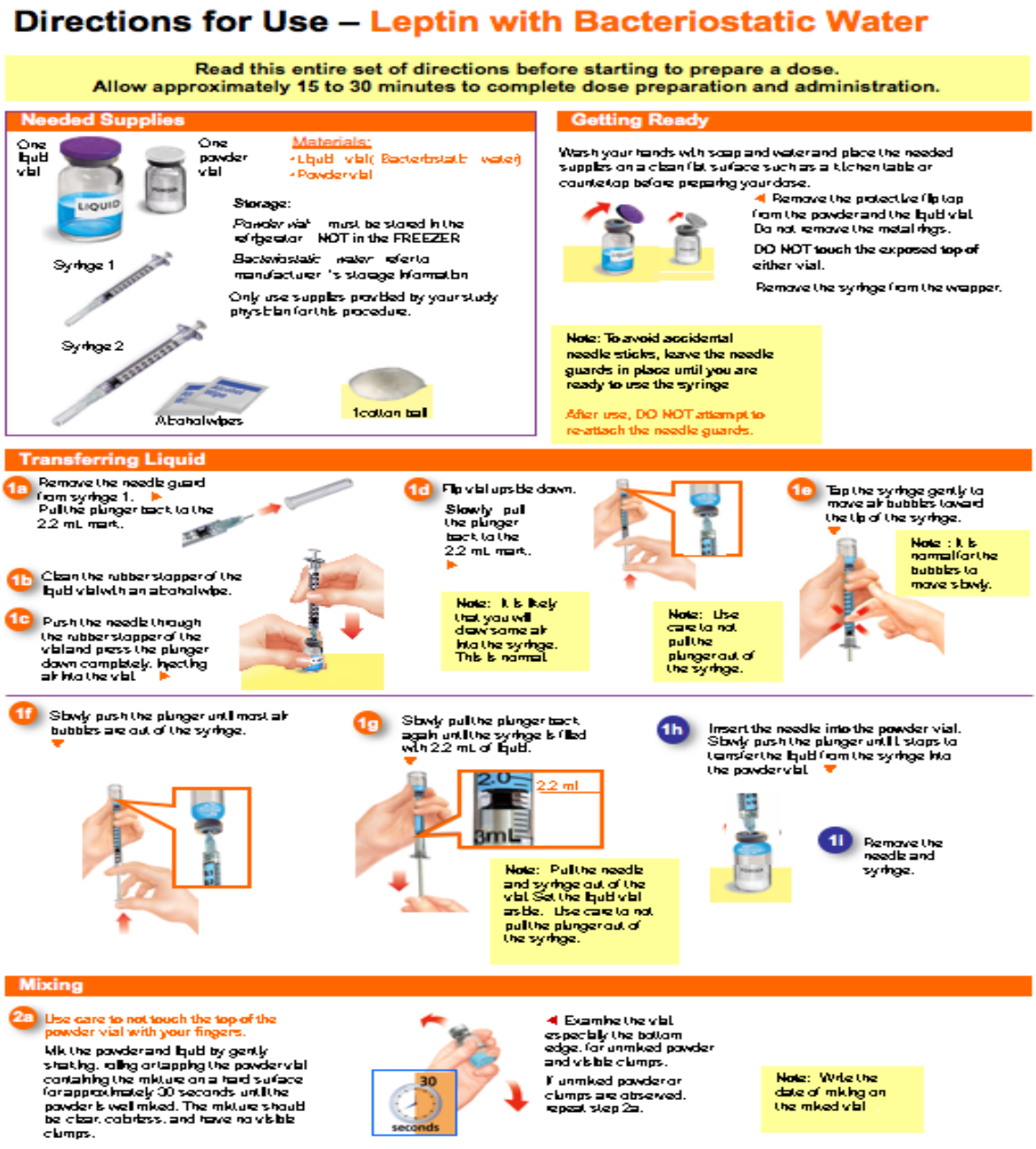
The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIDDK has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

## 11 REFERENCES

1. Cochran, E., et al., *Efficacy of recombinant methionyl human leptin therapy for the extreme insulin resistance of the Rabson-Mendenhall syndrome.* J Clin Endocrinol Metab, 2004. **89**(4): p. 1548-54.
2. Brown, R.J., E. Cochran, and P. Gorden, *Metreleptin improves blood glucose in patients with insulin receptor mutations.* J Clin Endocrinol Metab, 2013. **98**(11): p. E1749-56.

## APPENDIX 1: STUDY DRUG ADMINISTRATION

Injections at a single site will have a maximum allowable volume of 1.0 ml. Study medication should be administered preferably at the same time each day. The site(s) of injection should not occur on the limb from which subsequent blood draws will occur that day.



## Filling a New Syringe with the Mixture

3a Allow the mixed vial to reach room temperature prior to use.

NOTE: If the mixed vial is for more than 5 minutes, gently shake the vial to remix before proceeding.

3b Remove the needle guard from syringe 2.

3c Insert syringe 2 into the mixed vial.

3d Draw out the volume specified by your doctor following the procedure outlined in steps 1b to 1g.

## Dosing

4a Select one of the upper two quadrants of the abdominal region injection. Rotate between quadrants 1 and 2 for each dose. Clean the selected area using an alcohol wipe.


4b Using the technique recommended by hospital staff (with fold lift with the needle entering at a 90 degree angle), insert the needle into your skin and push in the plunger slowly as far as it will go.

DO NOT attempt to administer intravenously.

4c Wait for 5 seconds before withdrawing the needle.

4d Press a cotton ball over the injection site and massage gently for several seconds.

4e Discard needle and syringe.

4f Put the mixed vial back into the kit and return the kit to the refrigerator. NOT FREEZER.

**IMPORTANT:**

- **The mixed vial may only be used for a maximum of 3 days or until insufficient volume is left for another full dose.**
- **Do not mix content from one mixed vial with the content of another mixed vial.**

If you have other questions or problems,
Call your study physician for assistance.

[i] Taylor S. 1992. Lilly Lecture: Molecular mechanisms of insulin resistance – lessons from patients with mutations in the insulin-receptor gene. Diabetes, 41, 1473-1490.

[ii] Arioglu et al. 2002. Clinical course of the syndrome of autoantibodies to the insulin receptor (type B insulin resistance) – a 28-year perspective. Medicine, 81(2), 87-100.